

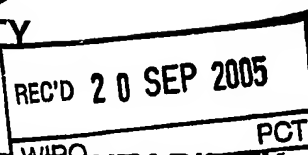
PATENT COOPERATION TREATY


PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 2003-100PC	FOR FURTHER ACTION See Form PCT/IPEA416	
International application No. PCT/DK2004/000242	International filing date (day/month/year) 02.04.2004	Priority date (day/month/year) 04.04.2003
International Patent Classification (IPC) or national classification and IPC C07J3/00, C07J31/00		
Applicant ALPHARMA APS et al.		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau) a total of 8 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in Item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input checked="" type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 04.11.2004	Date of completion of this report 19.09.2005	
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Samsam Bakhtiary, M Telephone No. +49 89 2399-8556	



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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-24 as originally filed

Claims, Numbers

1-23 received on 06.12.2004 with letter of 06.12.2004

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
 4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-23
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-23
Industrial applicability (IA)	Yes: Claims	1-23
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: WO 97/24365 A (GLAXO GROUP LTD ;BIGGADIKE KEITH (GB);
PROCOPIOU PANAYIOTIS ALEXAN) 10 July 1997 (1997-07-10)
- D2: WO 02/08243 A (COOTE STEVEN JOHN ;ROBINSON JOHN MALCOLM (GB);
GLAXO GROUP LTD (GB) 31 January 2002 (2002-01-31)
- D3: GB-A-2 088 877 (GLAXO GROUP LTD) 16 June 1982 (1982-06-16)
- D4: US-A-4 578 221 (BAIN BRIAN M ET AL) 25 March 1986 (1986-03-25)
- D5: WO 02/12265 A (COOTE STEVEN JOHN ; BIGGADIKE KEITH (GB); GLAXO
GROUP LTD (GB); NICE R) 14 February 2002 (2002-02-14)
- D6: HAPGOOD, JANET P. ET AL: "Steroid-affinity purification of the rat liver
glucocorticoid hormone receptor complex" JOURNAL OF STEROID
BIOCHEMISTRY (1987), 28(6), 769-77 CODEN: JSTBBK; ISSN: 0022-4731,
1987, XP001183044
- D7: HOYTE, R. M. ET AL: "Synthesis and evaluation of potential radioligands for the
progesterone receptor" JOURNAL OF MEDICINAL CHEMISTRY (1985),
28(11), 1695-9 CODEN: JMCMAR; ISSN: 0022-2623, 1985, XP001182782
- D8: MACINDOE, JOHN H. ET AL: "Comparative studies of 5.alpha.-reductase
inhibitors within MCF-7 human breast cancer cells" JOURNAL OF STEROID
BIOCHEMISTRY (1984), 20(5), 1095-100 CODEN: JSTBBK; ISSN: 0022-
4731, 1984, XP001182781
- D9: FORMSTECHER, P. ET AL: "Synthesis of steroidal 17.beta.-carboxamide
derivatives" STEROIDS (1980), 35(3), 265-72 CODEN: STEDAM; ISSN: 0039-
128X, 1980, XP001182780
- D10: KOLBE, ADELHEID ET AL: "Syntheses of dexamethasone conjugates of
the phytohormones gibberellin A3 and 24-epicastasterone" COLLECTION
OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS (2002), 67(1),
103-114 CODEN: CCCCAK; ISSN: 0010-0765, 2002, XP001194682
- D11: HEUBNER, ARNULF ET AL: "Application of liquid-liquid partition

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- chromatography in the simultaneous purification of sex-hormone-binding globulin and corticosteroid-binding globulin" JOURNAL OF CHROMATOGRAPHY (1987), 397, 419-34 CODEN: JOCRAM; ISSN: 0021-9673, 1987, XP001194688
- D12: PHILLIPPS G H ET AL: "SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS IN A SERIES OF ANTIINFLAMMATORY CORTICOSTEROID ANALOGUES, HALOMETHYL ANDROSTANE-17BETA-CARBOTHIOATES AND-17BETA-CARBOSELENOATES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 22, 1 October 1994 (1994-10-01), pages 3717-3729, XP002025925 ISSN: 0022-2623
- D13: MANZ, BERNHARD ET AL: "Synthesis of biotin-labeled dexamethasone derivatives. Novel hormone-affinity probes" EUROPEAN JOURNAL OF BIOCHEMISTRY (1983), 131(2), 333-8 CODEN: EJBCAI; ISSN: 0014-2956, 1983, XP009034828
- D14: GOVINDAN, MANJAPRA V. ET AL: "Three-step purification of glucocorticoid receptors from rat liver" EUROPEAN JOURNAL OF BIOCHEMISTRY (1980), 108(1), 47-54 CODEN: EJBCAI; ISSN: 0014-2956, 1980, XP009034821

2. Novelty

2.1 Intermediates claims 17-21; use of these intermediates claims 22,23

Documents D1, D3, D6-D11, D13 and D14 disclose steroid derivatives.

By introducing "disclaimers", it seems that now novelty may be recognised for these claims.

Compound 8 of D12 has been disclaimed (as originally filed)

2.2 Process claims 1-16

Documents D1-D5 and D12 disclose processes to make steroidal carbothioic acid or salts thereof by reacting the corresponding steroidal carboxylic acid with a coupling agent.

In claim 1 the coupling agent has been defined as carbodiimide (original claim 2).

None of the documents D1-D5, D12 disclose specific carbodiimide in the course of a specific process, then novelty for the process claims may be recognised.

3. Inventive step

The closest prior art may be considered to be D2 or D3.

The subject-matter of claim 1 therefore differs from this known D2 or D3 in that:

-D2, D3; coupling agent used is carbonyldiimidazole

-applic; coupling agent used is carbodiimide

The problem to be solved by the present application may be regarded as to provide an alternative process to make steroidal carbothioic derivatives starting with its corresponding steroidal carboxylic derivatives.

The solution proposed in claims 1-23 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

Document D1 suggests the use of an coupling agent (see page 12, lines 10 to page 13, lines 6) which may be a carbodiimide to transform a steroidal carboxylic acid of compound of formula (II) into an intermediate of formula (III) and then transforming the intermediate into a steroidal lactone of formula (I).

The skilled man starting with D2 or D3 and combining the technical teachings of D1 would obviously derive to the subject matter of claims 1-16.

Intermediates claims 17-21 and use claims 22-23 also lack of inventive step since the global process is not recognised as inventive.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D11, D13, D14 is not mentioned in the description, nor are these

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documents identified therein.

Re Item VIII

Certain observations on the international application

1. In claim 17, the definition of the group Z is not clear, and this in the sense to how the linkage of the groups D-G to the steroidal core are done.
2. In case this application is proceeded in the european phase, we draw the attention of the Applicant to the new jurisprudence concerning "disclaimers".